[Frontiers in Bioscience 8, b1-5, January 1, 2003]

COLONIC PACING IN THE TREATMENT OF PATIENTS WITH IRRITABLE BOWEL SYNDROME: TECHNIQUE AND RESULTS

Ahmed Shafik [1], Olfat El-Sibai [2], Ali A. Shafik [3], Ismail Ahmed [3]

[1] Professor and Chairman, Department of Surgery and Experimental Research, Faculty of Medicine, Cairo University, Cairo, [2] Professor and Chairman, Department of Surgery, Faculty of Medicine, Menoufia University, Shebin El-Kom, [3]Lecturer in Surgery, Department of Surgery and Experimental Research, Faculty of Medicine, Cairo University, Cairo, Egypt

TABLE OF CONTENTS

1. ABSTRACT

The treatment of the irritable bowel syndrome (IBS) is not entirely satisfactory as the exact cause of the condition has not been revealed. We have demonstrated in a recent study that the IBS exhibited a "tachyarrhythmic" electromyographic pattern; the wave rhythm was irregular and wave variables were higher than those of the healthy volunteers. We suggested that a disorder of the colonic pacemaker discharges these abnormal waves thereby causing the motor disorders of IBS. In another study, we determined the colonic pacing parameters needed to modulate the disordered pacemaker. In the current communication we investigated the effect of colonic pacing, using these parameters, on the EMG activity of the sigmoid colon (SC) and on the clinical manifestations of patients with IBS. A pacemaker was implanted in a subcutaneous pocket in the inguinal area and its two leads were hooked to the colosigmoid junction. The effect of colonic pacing on the SC EMG activity was investigated by inserting two recording electrodes into the SC muscle. The patients were then trained for home pacing after removal of the 2 recording electrodes. Nine patients (age 42.7±4.2 years, 6 women) with IBS were studied. The pre-pacing tachyarrhythmic pattern of EMG was recorded. On colonic pacing, the slow wave rhythm became regular and wave variables were normalized; the symptoms of the IBS improved. The optimal parameters used for pacing comprised an amplitude of 6 mA, a pulse width of 150 ms and a frequency of 25% higher than that of the basal colonic waves. In 7/9 patients the improvement of symptoms continued when pacing was ceased after 6 months of daily pacing; the pacemaker was removed after 3 months of non-pacing. In 2/9 patients, pacing needed to be continued because the symptoms recurred each time the pacing was ceased. In conclusion, colonic pacing succeeded in normalizing the tachyarrhythmic pattern and relieving the symptoms of the IBS. No complications were encountered and the method was well accepted and tolerated. Further studies on a large group of patients are required.

2. INTRODUCTION

Irritable bowel syndrome (IBS) is not an uncommon disease. The patients complain of abdominal pain with or without alterations in bowel habits but do not show any anatomical abnormality on diagnostic testing (1-5). There is a wide variety of complaints; more than 90% of the patients present with 2 or more of the following: feeling of abdominal distension, increased frequency of bowel movements with the onset of abdominal pain, loose stools with onset of pain, and relief of pain with defecation (6). The most typical complaint is a crampy diffuse abdominal pain which is associated with alternating constipation and diarrhea or postprandial urgency (1).

The etiology of IBS is hitherto unkown (1-6). It has been related to disorders of motility or perception of the lower gut (2-7). Other factors as behavioral, psychological

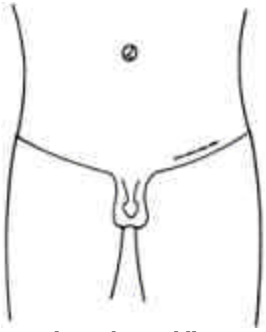

Figure 1. Incision along the middle one-third of, and 2 cm above, the inguinal ligament.

or mucous membrane disorders and food intolerance may be also involved in some cases (8-11).

We recently studied the electromyographic activity of IBS (unpublished data). It showed a "tachyarrhythmic pattern"; the frequency, amplitude and conduction velocity of the slow waves were significantly higher than in the healthy volunteers and the rhythm was irregular. Fast activity spikes or action potentials (APs) followed or were superimposed on the slow waves (SWs); they were inconsistent and occurred randomly. The sigmoid colon pressure was significantly higher in IBS patients if compared to that of the healthy volunteers (6,7, and unpublished data). Action potentials were coupled with bouts of pressure increase which was significantly higher than that recorded in the normal controls. The study suggested that the cause of the IBS is related to an aberrant focus in one or more of the colonic pacemakers. Colonic electric activity seems to regulate the colonic motility which is presumably impaired by a disorder affecting the electric waves (12,13). This was evident from the electrosigmoidograms of the various pathologic lesions of the SC in which the electric waves with low variables (frequency, amplitude and conduction velocity) were associated with diminished colonic motility (13).

Further studies have demonstrated that the colon possesses at least 4 pacemakers which generate the electric activity to the colon (14). They are located at the cecal pole, the cecocolonic junction, the mid-transverse colon and at the colosigmoid junction (CSJ).

The treatment of patients with IBS is problematic and the results are in most cases unsatisfactory (1-5). Actually, there is so far no curative treatment available for IBS. The tachyarrhythmic pattern of the EMG activity of the SC seems to be responsible for the disordered motile activity in the IBS, the associated abdominal pain and the bowel irregularities (unpublished data). Electric waves of the SC have been demonstrated to start at the CSJ and to spread caudad along the SC; a CSJ pacemaker is thought to initiate and regulate the SC electric and motor activity (12-14). In a recent study (unpublished data), we have defined the colonic pacing parameters that are required to modulate the "tachyarrhythmic" pattern of the SC; colonic pacing using these parameters has normalized the tachyarrhythmic waves.

In the current communication we studied the effect of colonic pacing on the EMG activity of the SC and on the clinical manifestations of patients with IBS.

3. MATERIAL and METHODS

3.1. Subjects

The study comprised nine patients with IBS who gave an informed consent before enrolment in the study. The mean age was 42.7±4.2 SD years (range 35-54); 6 were women and 3 men. They complained of diffuse abdominal pain which was relieved by defecation. All patients had loose stools and a feeling of abdominal distension or bloating, and 4/9 had in addition the feeling of incomplete evacuation with urgency. The mean duration of the symptoms was 10.6± 4.8 SD years (range 6-14). The patients had followed various medical regimens for long periods with temporary improvement.

Physical examination including neurologic assessment was unremarkable. Laboratory work as well as proctoscopy, colonoscopy and barium enema studies were normal.

3.2. Methods

3.2.1. Pacemaker application

After the patients had fasted for 12 hours, the colon was emptied by means of saline enema. The pacemaker (Prevail, Medtronic, Minneapolis, Minn., USA) was implanted in a subcutaneous pocket in the inguinal area. Two leads were jointly passed subcutaneously from this area to the anal orifice and then through the anal canal, rectum and SC to be hooked to the CSJ. Under general anesthesia, a 4-cm incision was performed 2 cm above and parallel to the mid one third of the inguinal ligament (Figure 1). We dissected in the subcutaneous space to shape a pocket for the pacemaker. A tunnel was then created by means of a dissecting forceps that was passed subcutaneously from the pocket alongside the scrotum or labium majus to the anal orifice where a 1-cm incision was performed in the painless anal mucosa 5 cm orally to the anal orifice. A long artery forceps was advanced subcutaneously through the incision until it appeared in the pocket. The tips of the leads were grasped with the forceps and pulled through the tunnel to emerge from the anal incision. The leads, now in the gut lumen, were then directed orally under sigmoidoscopic and fluoroscopic control until they reached the CSJ where they were hooked; they lay on the mucosal surface of the gut. The patient left the hospital 24 hours after surgery. An analgesic was given on the first post-operative day and a quinolene antibiotic for two days.

3.2.2. Determination of the myoelectric activity: basal and during pacing

This experiment was done to test the effect of colonic pacing on the EMG activity of the SC. The patients were allowed 7-10 days to recover from surgery. After fasting for 12 hours, the colon was evacuated by saline enemas. The SC EMG was recorded by 2 electrodes similar to that described above. They were introduced per anum

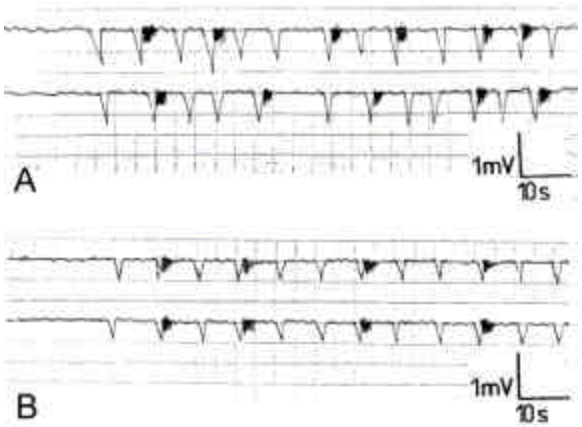

Figure 2. Electrosigmoidogram from a patient with irritable bowel syndrome: A) before pacing showing a "tachyarrhythmic pattern". The slow waves have an irregular rhythm and a higher frequency, amplitude and conduction velocity than those of the healthy volunteers. Action potentials occurred randomly. B) during pacing showing the slow waves having a regular rhythm and lower variables than before pacing.

and hooked to the wall of the SC under sigmoidoscopic and fluoroscopic control. One electrode was applied to the SC 3-5 cm aborally to the CSJ and the 2nd electrode 5-7 cm orally to the RSJ. Recording was started 20 minutes after placing the electrodes so that the SC would have adapted to the presence of the electrodes. Waves registered from the 2 electrodes were amplified using an AC amplifier with a frequency response of ± 3dB from 0.016Hz to 7 kHz and were displayed on the UV recorder at a sensitivity of 1 mV/cm. The basal colonic EMG activity was recorded for 20 min. followed by another 20 min. of recording during pacemaker stimulation. Previously defined SC pacing parameters consisted of an amplitude of 6 mA, a pulse width of 150 ms and a frequency of 25 % higher than that of the already recorded basal colonic waves (unpublished data). The pacemaker was programmed at pace rate and time.

3.2.3. Home pacing

After we had tested the effect of colonic pacing on the SC EMG activity, we removed the 2 recording electrodes, leaving the stimulating electrodes connected to the inguinally placed pacemaker. The patient was then trained for using the pacemaker by himself. As the abdominal pain was most often postprandial, the patients were instructed to perform colonic pacing after meals and to record the daily number of pain attacks, bowel evacuations, stool consistency and the need for the use of pain killers (anticholinergics and spasmolytics). The patients were asked to return in one-monthly internals for follow-up which comprised clinical assessment of the daily recordings and examination of pacemaker and leads. The mean follow up period was 15.3 ± 1.4 months (range 13-18).

The results were analyzed statistically using the analysis of the variance (ANOVA), and values were given as the mean ± standard deviation. Differences of $p<0.05$ were taken as statistically significant.

4. RESULTS and DISCUSSION

No adverse side effects were encountered during or after application of the pacemaker or the electrodes and all of the patients were evaluated.

Before pacing, the basal electric activity of the SC exhibited a "tachyarrhythmic pattern". The slow waves showed an irregular rhythm and the SW variables were not the same from the two recording electrodes of the individual patient (Figure 2, A). Fast activity spikes or APs followed or were superimposed on the SWs (Figure 2, A). They had an irregular rhythm and occurred randomly. The SW frequency, amplitude, and conduction velocity are shown in table 1 (Figure 2, A). These variables were significantly higher than those recorded from the healthy volunteers ($p<0.05$) (12,13).

During colonic pacing using the aforementioned parameters, the SWs had a regular rhythm. As shown in table 1 (Figure 2, B), the SW variables exhibited a significant reduction ($p<0.05$) if compared to those before pacing (table 1). These variables were the same from the 2 electrodes of the same patient. Slow waves were followed or superimposed by APs which occurred randomly (Figure 2, B).

4.1. Effect of colonic pacing on the clinical manifestations of the IBS

Colonic pacing was performed 2 to 3 times per day (mean 2.6 ± 0.8), commonly post-prandially upon the feeling of abdominal pain. It was also performed between the meals when pain was felt. The abdominal pain was ameliorated 2 to 5 min post-pacing and disappeared 5-10 min. later; when pacing was ceased after 10-15 min the pain returned within the following 10-15 min. Pacing for 30 to 40 min. eliminated the pain for 5-8 hours to approximately the next meal as reported by the patients. All of the 9 patients did colonic pacing 3 times per day at the start of the treatment, i. e. pacing was done after each meal. After one month into pacing, 7 of the 9 patients observed that the abdominal pain disappeared with breakfast pacing to re-appear following supper. Therefore, they reduced colonic pacing to twice/day: after breakfast and after supper. Two to 3 months later, the occurrence of abdominal pain after breakfast only, cut the number of daily pacings to one after breakfast. All of the 7 patients discontinued colonic pacing 6 months from the start because they no longer felt any abdominal pain.

Defecation disorders comprising loose stools, the feeling of urgency and bloating showed partial improvement during the first 2 months of colonic pacing, while by the 6th month the stool character was normalized and the bloating sensation would have disappeared. Thus, after six months of pacing, 7 patients were free of abdominal pain and had a normal stool character; they discontinued colonic pacing and remained pain-free with a normal stool character for 3 months after pacing was ceased. For this reason,

Table 1. Slow wave variables (frequency, amplitude and conduction velocity) before and during pacing of patients with irritable bowel syndrome [1]

	Frequency (cycle/min)		Amplitude (mV)		Velocity (cm/s)	
	Mean	**Range**	**Mean**	**Range**	**Mean**	**Range**
Before pacing	6.2 ± 1.1	5 – 9	0.8 ± 0.3	0.7 – 1.1	6.9 ± 1.8	6 – 8
During pacing	4.2 ± 1.2 [2]	3 – 7	0.6 ± 0.1 [2]	0.5 – 0.8	4.3 ± 1.1 [2]	3.8 – 6

[1]values were given as the mean ± standard deviation (SD). [2]$p<0.05$ P values during pacing were compared to that before pacing.

the pacemaker and the electrodes were removed. The embedded pacemaker was taken out under local anesthesia, and the skin incision was sutured. The leads were removed under sigmoidoscopic control. No complications occurred. The 7 patients are meanwhile 4 to 6 months after pacemaker removal without pain and with normal defecation.

The remaining 2/9 patients are still using colonic pacing since 13 and 18 months, respectively. Pacing is being done once or twice per day, but mainly after supper. In these 2 patients abdominal pain would occur after supper and only occasionally after breakfast, and would be mild during the rest of the day. When after 6 months of pacing we asked the two patients to halt colonic pacing for 10 days in order to test whether the abdominal pain would persist, the pain still occurred regularly after supper and the patients restarted performing colonic pacing. We repeatedly examined the pacemakers and electrodes for technical errors but found them working properly. Upon reviewing the history and the investigations that had been done for these two patients, we found that they had the longest history of the disease: 12 and 14 years of duration, respectively, and the highest SW variables: frequency 7 and 9 cycles/min, amplitude 1.0 and 1.1 mV, and conduction velocity 7.4 and 7.8 cm/s, respectively. The two patients are continuing with the colonic pacing and did not ask for pacemaker removal.

The technique was well tolerated and accepted by the IBS patients. We did not encounter infection at the site of the pacemaker nor lead migration in any of the patients.

No curative treatment is so far available for the IBS. The results of the known therapeutic options are still not entirely satisfactory (1-5). The symptoms of the IBS which comprise mainly the crampy abdominal pain and the defecation disorders are presumably attributable to colonic motor dysfunction. This is evident from the tachyarrhythmic pattern recorded in the IBS patients which most likely denotes a colonic motor dysfunction. Thus, we believe that correction of the tachyarrhythmic pattern of the IBS would correct the motile activity of the colon and result in disappearance of the symptoms.

The colon exhibits electric activity in the form of SWs and APs (12,13,15-18). These waves are apparently discharged from colonic pacemakers (12-14); four pacemakers could be identified in the colon (14). The results of a recent study have suggested that the tachyarrhythmic pattern of the IBS is due to a dysfunctioning colonic pacemaker (unpublished data). Given that the IBS affects mainly the left colon and in particular the SC and in 20-50% the rectum (3,4,7), we selected the CSJ pacemaker and postulated that its electromodulation would normalize these tachyarrhythmic waves and relieve the symptoms of the IBS. Upon pacemaker stimulation, we noted that the wave rhythm became regular while frequency, amplitude and conduction velocity were diminished to be similar to the mean normal values of the colonic electric waves in our laboratory (12,13).

Our recent studies (unpublished data) have suggested that the elevated SW variables recorded in the IBS as well as the significant increase of APs compared to the healthy volunteers could explain the high basal colonic pressure which is reported in the IBS and which probably leads to the diffuse abdominal pain. Meanwhile, the crampy abdominal pain, characteristic of the IBS (1-5), appears to be the result of the high colonic pressure bouts associated with the APs. These cramps occurred randomly as the APs also occur randomly. We have recently demonstrated that normalization of the colonic electric activity could correct both the basal and episodic colonic pressure (unpublished data). Thus the improvement of the diffuse and crampy abdominal pain which occurred in the studied patients after colonic pacing seems to be related to normalization of the colonic pressure both the basal and the one occurring in bouts coupled with APs. On the other hand, improvement of the stool character upon pacing appears to be related to improvement of colonic electric and motor activity. All of the 9 patients in the current study had loose stools pre-pacing, due presumably to the elevated SW variables and increased colonic motor activity. The diminished electric and probably motor activity post-pacing seems to delay stool evacuation and inhibit the feeling of urgency.

At the start, pacing was performed after each meal, but the sessions gradually diminished until, after 6 months, 7/9 patients were not in need of pacing because the symptoms of the IBS had disappeared. The patients remained symptomless without pacing. It seems likely that repeated pacing modulated the disordered pacemaker and normalized the electric waves delivered to the SC. Moreover, it may be assumed that the repeated electromodulation of the CSJ pacemaker has activated the colonic musculature so that spontaneous normalization of the colonic electric activity occurred without pacing.

In two of the nine patients pacing could not be weaned yet. Although pacing had normalized the colonic electric waves and ameliorated the symptoms of the IBS in both patients, the symptoms recurred when pacing was ceased. The reason why weaning of the pacing procedure was so far unsuccessful in these 2 cases is not exactly known. It may be due to either the reportedly longest duration of the IBS in these 2/9 patients, or to their SW

variables which were the highest in the test group, or to both.

In conclusion, colonic pacing succeeded in normalization of the tachyarrhythmic pattern of the SC and in aborting the symptoms of the IBS in all the patients studied. In 7 patients pacing was performed for 6 months and when ceased, the IBS symptoms did not recur, thus allowing for the removal of the pacemaker. In the remaining 2 patients, pacing continued to avoid recurrence of the symptoms. No complications were encountered. Colonic pacing seems to be suitable for IBS treatment when other simpler methods have failed to cure the condition. However, not before a large number of patients has been treated with pacing will the technique be included as a therapeutic option for the IBS.

5. ACKNOWLEDGMENT

Margot Yehia and Waltraut Reichelt assisted in preparing the manuscript

6. REFERENCES

1. Petrini, J.L.: Diet and drugs in colorectal surgery. In: Colon & Rectal Surgery. Ed: Corman M.L. 4th edn. Philadelphia, Lippincott-Raven, USA.37-45 (1998)
2. Collins, S.M.: Is the irritable gut an inflamed gut? *Scand J Gastroenterol* 192 (suppl), 102-105 (1992)
3. Heaton, K.W., L.T.D. O'Donnell, F.E.M. Bradden, R.A. Mountford, A.O. Hughes & P.J. Cripps: Symptoms of irritable bowel syndrome in a British urban community: consulters and non-consulters. *Gastroenterology* 102, 1962-1937 (1992)
4. Kay, L., T. Jorgensen & K.H. Jensen: The etiology of the irritable bowel syndrome in a random population: prevalence, incidence, natural history and risk factors. *J Intern Med* 236, 23-30 (1994)
5. Kettell, J., R. Jones & S. Lydeard: Reasons for consultation in irritable bowel syndrome: symptoms and patients characteristics. *Br J Gen Pract* 42, 459-461 (1992)
6. Manning, A.P., W.G. Thompson, K.W. Heaton & A.F. Lorris: Towards positive diagnosis of the irritable bowel. *Br Med J* 2, 653-654 (1978)
7. Munakata, J., B. Naliboff, F. Harraf, A. Kodner, T. Lembo, L. Chang, D.H. Silverman & E.A. Mayer: Repetitive sigmoid stimulation induces rectal hyperalgesia in patients with irritable bowel syndrome. *Gastroenterology* 112, 55-63 (1997)
8. Creed, F. & E. Guthrie: Psychological factors in the irritable bowel syndrome. *Gut* 28, 1307-1318 (1987)
9. Walker, E.A., W.J. Katon & P.P. Roy-Byrne: Irritable bowel syndrome and psychiatric illness. *Am J Psych* 147, 565-572 (1990)
10. Hislop, I.G.: Psychological significance of the irritable colon syndrome. *Gut* 12, 452-457 (1971)
11. Drossman, D.A., J. Leserman, G. Nachman, Z.M. Li, H. Gluck, T.C. Toomey & C.M. Mitchell: Sexual and physical abuse in women with functional or organic gastrointestinal disease. *Ann Intern Med* 113, 828-833 (1990)
12. Shafik, A.: Transcutaneous electrosigmoidography. Study of the myoelectric activity of sigmoid colon by surface electrodes. *Front Biosci* 1, b1-4. PubMed #9159196 (1996)
13. Shafik, A.: Electrosigmoidogram in the various pathologic conditions of the sigmoid colon. *Front Biosci* 3, b11-14. PubMed #9778540 (1998)
14. Shafik, A., O. El-Sibai & A.A. Shafik: Electrophysiologic identification of the location of the colonic pacemakers. A human study. *Front Biosci* 7, b1-5 (2002)
15. Abo, M., T. Kono, C.L. Lu & J.D. Chen: Effects of caffeine on gastrointestinal myoelectric activity and colonic spike activity in dogs. *Scand J Gastroenterol* 33, 368-374 (2000)
16. Aube, A.C., C. Cherbut, M. Barbier, J.H. Xing, C. Roze & I.P. Galmiche: Altered myoelectric activity in noninflamed ileum of rats with colitis induced by trinitrobenzene sulphoric acid. *Neurogastroenterol Motil* 11, 55-62 (1999)
17. Dapoigny, M., J.F. Trolese, G. Bommelaer & R. Tournut: Myoelectric spiking activity of right colon, left colon and rectosigmoid of healthy humans. *Dig Dis Sci* 33, 1007-1012 (1988)
18. Frexinos, J., L. Bueno & J. Fioramonti: Diurnal changes in myoelectric spiking activity of the human colon. *Gastroenterology* 88, 1104-1110 (1985)

Key Words: Slow waves, Action potentials,Tachyarrhythmia, Pacemaker; Electromyography

Send correspondence to: Ahmed Shafik, MD, PhD, 2 Talaat Harb Street, Cairo 11121, Egypt, Tel/Fax: +20-2-7498851, E-mail: ashafik@ahmedshafik.org